

A Few Words about Parkinson's Disease

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Parkinson's disease is a progressive central nervous system disorder. The main symptoms of the disease were originally described in 1817. by a British physician dr. James Parkinson, who calls it a tremendous paralysis. Only in the 1960s pathological and biochemical changes in the brain of patients have been identified, which opens the way for the first effective remedy for this disease.

Keywords: Parkinson's Disease, Parkinsonism, Therapy

Introduction

The aim of a neurological history and examination is to locate the area of damage within the nervous system and then, on the basis of the tempo of the history, to make an attempt at diagnosis [1].

The nervous system comprises the cerebral cortex, brain stem, cerebellum, spinal cord, roots and peripheral nerves. The term 'neuraxis' is often used to encompass the cerebral cortex, brain stem, cerebellum and spinal cord, alternatively known as the central nervous system (CNS) in contradistinction to the spinal nerve roots and the nerves which they eventually form, the neuromuscular junction and muscle, which collectively is known as the peripheral nervous system (PNS).

Information is received into the brain via the senses (vision, hearing, smell, touch). The response from the nervous system to stimuli perceived by the senses is either in the form of speech or movement. On this basis, there are therefore major ascending pathways within the spinal cord, brain stem and cortex which convey information from the periphery to the brain.

Similarly, there are major pathways within the brain conveying information from vision to the appropriate part of the brain which deals with the vision in the occipital cortex. The major motor pathway runs from the cortex down through the brain stem and spinal cord, and ends on the anterior horn cells on the peripheral nerves. Activation of this pathway produces movement.

The brain can therefore be considered as a 'wiring diagram' with descending pathways, ascending pathways and horizontal pathways which, within the brain, are the cranial nerves and, in the spinal cord, are the nerve roots. Attempting to make a diagnosis, therefore, is often a matter of identifying the point of intersection between ascending and descending pathways and horizontal pathways.

Neurological symptoms

The medical profession in its training as well as in everyday practice takes a fundamentally therapeutic attitude to its patients [2]. The aim is perceived to be the diagnosis and assessment of injury or illness; and its restitution to the maximum extent possible. However, in the medico-legal context the role of the medical expert is quite different. He is seeing the "patient" in order to evaluate the effect that injury has caused and to provide a prognosis which will allow the court to come to a decision about the magnitude of compensation. By the time most claims come to settlement therapeutic aspects are generally long past. The practical therapeutic approach of medicine therefore may lead to conflicts which should be perceived by the doctor.

In the assessment of any patient complaining of neurological symptoms some general principles must be borne in mind. Neurological symptoms may be associated with objective abnormality demonstrable on examination. But the objective signs may be disproportionate, that is, they may be less than the

symptoms would lead you to expect so that wilful or subconscious exaggeration is suspected. Or the signs may seem unrelated to the symptom, for example, a complaint of paralysis when the signs indicate sensory loss. Or finally the neurological symptoms may have no corresponding sign or abnormality on examination. A lack of objective support for the organic basis of a complaint is relatively common in neurology. It occurs, for example, in many pain syndromes, especially those where the pain is associated with damage to peripheral nerve, the spinal cord or central nervous system. Migraine, epilepsy, irritability and personality change are all common post-traumatic phenomena where there is usually no associated objective abnormality. Compensation gives a motive to perpetuate symptoms previously experienced or to claim symptoms that have either recovered or never been sufficiently severe to cause disability.

The doctor must be able to recognise patterns of symptomatology associated with organic disorder of the CNS and to be able to distinguish these from symptoms that are exaggerated or feigned. Where there are abnormalities demonstrable on examination the case may appear straightforward and convincing but there should be an "appropriateness" between history, present symptoms and objective abnormality.

Despite the large numbers of individuals affected, members of the general public often have little insight into the consequences of a neurological condition until they have direct personal experience [3]. Levels of awareness are low even about relatively common conditions such as epilepsy and head injury. Conditions that are less common, such as Friedreich's ataxia, are largely unheard of and poorly understood by both the general public and health and social care professionals alike. Research commissioned to underpin the National Service Framework (NSF) for Long-term Conditions demonstrates the fear felt by patients who perceive that the professionals organising and delivering their care have little understanding of their particular needs. Individuals with conditions affecting their ability to communicate are particularly vulnerable and often disadvantaged by the failure of staff to recognise the extent to which this problem affects care. Similarly, busy staff may wrongly interpret cognitive and behavioural problems and attribute any difficulties to personality defects, failure to adjust or obstinacy. These labels once acquired are often difficult to shake off, becoming accepted and perpetuated by other health professionals without further investigation or assessment.

In this way the ignorance and attitudes of others can compound the difficulties people with neurological conditions experience, often causing them to feel stigmatised and misunderstood, which can, in turn, lead to further social, emotional and economic disadvantage.

Neurodegenerative disorders

Impairment of competency, or decision-making capacity, is an inevitable consequence of neurodegenerative dementias like Alzheimer's disease (AD) and Parkinson's disease (PD) [4]. As capacities for memory, judgment, reasoning, and planning erode, AD patients eventually lose decision-making capacity in every sphere of life. Specific competencies that are lost include the capacity to make medical decisions, to consent to research, to manage financial affairs, to execute a will, to drive, to manage medications, to live independently, and ultimately to handle even the most basic activities of daily life. Patients with Parkinson's disease and dementia have demonstrated deficits in medical decision-making capacity and are likely to be impaired in other higher order capacities such as financial management. Loss of competency in dementia has important consequences for patients and their families, for health care and legal professionals, and for society as a whole.

There are a number of degenerative syndromes less common than Parkinson's disease in which parkinsonism occurs and for which care requires similar considerations [5]. Each of these conditions may have a particular emphasis in its mix of symptoms. Patients with multiple system atrophy (MSA), for example, are more likely to have troublesome urinary incontinence compared with Parkinson's disease patients and MSA more often causes early erectile dysfunction. Other syndromes include progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB), corticobasal degeneration (characterized by asymmetric parkinsonism) and Parkinson's disease with dementia (PDD). These conditions do not, on the whole, respond to therapy as well as does Parkinson's disease, and their 'atypical' nature may become clearer through a lack of response to levodopa (L-dopa).

Parkinson's disease

Parkinson's disease is a common disorder, the incidence rising after the age of 50 to somewhere between 1–2% of the ageing population [1]. Presentation is usually between the ages of 55 and 70, and the onset is rarely, if ever, dramatic. In the majority of patients, there is a slow insidious onset of tremor, stiffness and

clumsiness, typically affecting one upper limb. The voice becomes softer and may become slurred (dysarthria), and there may be difficulty in walking. Although the disease can remain confined to one side of the body for many years, it classically spreads to involve both sides of the body over a period of several years.

The typical patient has a mask like expression with a soft monotonous voice, they walk with slow small steps (march au petite pas), with impairment of arm movement. The greatest difficulty is in initiating movement, for example, walking or getting out of a chair, and the patient often tends to 'freeze' when trying to go through an open door or when turning.

The majority of patients with Parkinson's disease have a tremor which is often described as 'pill rolling' because of its rhythmicity. It is important to recognise, however, that not all patients with a tremor have Parkinson's disease. The diagnosis of Parkinson's disease is entirely clinical. There are no specific aids to diagnosis, as in other diseases where the diagnosis is clinical. This allows scope for considerable diagnostic variability.

Parkinson's disease is due to a lack of dopamine in the striatum (part of the basal ganglia) and treatment is therefore directed to replace the missing endogenous dopa with exogenous dopa. In the early stages of the disease, this causes few or no problems. However, the longer drug therapy is continued, the more drug induced side effects will develop. This implies that the management of patients with Parkinson's disease should only be undertaken by those with specific experience in the field which, unfortunately, is not always the case.

Parkinson's disease (PD) is a progressive loss of dopaminergic neurons in the substantia nigra and other brain stem nuclei [6]. Patients with PD have motor impairment with resting tremor, bradykinesia, and rigidity, but also balance problems and autonomic nervous dysfunction, and they show cognitive and psychiatric features. Genetic contributing factors include mutations in the α -synuclein (PARK1) and parkin (PARK2) genes. Parkin functions as an E3 ubiquitin-protein ligase, and a loss of function results in the failure of intracellular protein processing, with consecutive accumulation of various proteins to toxic levels. Although sporadic and inherited PD have different causes, they probably intersect in common pathways. The central cause of sporadic PD seems to be a mitochondrial complex I inhibition, and complex I deficiency may cause α -synuclein aggregation, contributing to the degeneration of dopaminergic neurons.

As major depressive episodes may occur in someone with a bipolar disorder, the diagnosis of bipolar disorder should always be considered when evaluating someone with depressive symptoms [7]. A depressed person with a prominent irritable mood (rather than expressed sadness) may also be difficult to distinguish from manic episodes with irritable mood or mixed features. A mood disorder due to a general medical condition is also a possibility until medical conditions are ruled out. Hypothyroidism, multiple sclerosis, and Parkinson disease are some common conditions that may cause depressive symptoms. Substance/medication-induced depressive disorder should also be considered in someone actively using or withdrawing from a substance use. Perhaps less of a concern in the older adults, but not rare, some symptoms in attention-deficit/hyperactivity disorder also overlap with depression—namely, distractibility and low frustration tolerance, manifested as irritability. As well, some personality disorders (particularly borderline personality disorder) may also have overlapping symptoms with depressive disorders. In a person presenting with psychotic symptoms in addition to their mood symptoms, a schizophrenia spectrum disorder may be considered. In a geriatric depressed patient with cognitive deficits, neurocognitive disorders would be a consideration.

Parkinsonism

Parkinsonism refers to a clinical condition that consists of tremor, rigidity and bradykinesia in the absence of Parkinson's disease [8]. Loss of dopaminergic input to the striatum causes the rigidity and bradykinesia. Thalamic, cerebellar and basal ganglia abnormalities are the probable cause of thalamocortical oscillations underlying the resting tremor. The prevalence of parkinsonism was 3% in a large sample of people with developmental disability (n=1227), which was higher than that in general population, and increased with age and male gender.

The majority of parkinsonism observed in people with ID is drug-induced. The commonest causative agent is a conventional antipsychotic while tetrabenazine, tricyclic antidepressants and selective 5-hydroxytryptamine (5-HT, serotonin) reuptake inhibitors have also been reported to be associated with this problem. Clinical presentations closely resemble Parkinson's disease, although symmetric involvement at onset and the presence of akathisia or dyskinesia help to distinguish the former from the latter. Drug-induced parkinsonism may continue up to one year after the drug is withdrawn.

In adults with Down syndrome who develop Alzheimer's disease, 20% were reported to show flexed posture, bradykinesia, masked face and cogwheel rigidity of parkinsonism in their late stage.

Diagnosis

Parkinson's disease is diagnosed by a careful neurological examination, testing movements, coordination, reflexes, and other aspects of function [9]. If the physician suspects PD, the patient will usually be referred to a neurologist for definitive diagnosis. Unilateral (one-sided) tremor, slowed movements, and muscle stiffness are generally enough to confirm the diagnosis; two of the three are usually considered definitive. Several specialized tests may be used, including imaging of the brain with magnetic resonance imaging (MRI) or positron emission tomography (PET). These are not essential to diagnosis in most cases, but may help to confirm the diagnosis in difficult cases and to distinguish PD from similar diseases such as progressive supranuclear palsy, corticobasal degeneration, or multiple system atrophy. Clues that the disease is one of these, rather than PD, include early or rapidly progressing dementia, loss of coordination, or early and prominent orthostatic hypotension (lightheadedness upon standing).

Therapy

Physical therapy, including passive and active mobilization exercises, walking, and range of motion exercises, when combined with medication treatment, may be superior to medication treatment alone [6]. Many rehabilitative therapies, such as speech therapy and music therapy, have been studied in Parkinson's patients. All have shown improvements in functioning during treatment, but many report that the positive gains are not maintained once the treatment concludes. There have been no randomized, controlled trials showing long-term, sustained effects on function from rehabilitation alone. Hence, the physical treatment of Parkinson's disease can be considered an example of "preventive" geriatric rehabilitation.

The patient should be trained in techniques used to counter the effects of the disease. Strengthening and endurance training and proper use of assistive equipment also are important. Such training is best provided early in the course of the illness as an outpatient. Involvement in a support group may help to maintain newly learned skills.

Gait and balance training emphasizes a safe gait and improved balance. The patient should be taught to keep the head up, to counter the flexed posture consciously, and to lift the toes during the swing phase of the gait. It also may help to take longer steps and widen the base. The therapist often prescribes a home program of regular exercises to maintain or improve strength, range of motion, and flexibility. Other patients find singing to be helpful. In a recent 3-month randomized, controlled, single-blinded study, researchers explored the efficacy of active music therapy (MT) on motor and emotional functions in Parkinson's patients. The MT group showed significant improvements in their bradykinesia, as measured by the Unified Parkinson's Disease Rating Scale.

Gene therapy

Concerning the brain anatomy, the brain is surrounded by various barriers [10]. First, at the gross morphological level it is enclosed by the bony skull and fibrous meninges. At the cellular level it is separated from the general bloodstream by a selective blood-brain barrier. At the functional level, the brain possesses a peculiar immune reactivity whose understanding remains to be dissected completely. This peculiar immune status of the brain is usually mislabeled as the brain's immune privilege. However, the brain is not immune-privileged in the naive manner of this description. The main limitation is to prime an immune response from antigens expressed exclusively within the brain parenchyma. This is an advantage for gene therapists. However, any antigen that primes the immune system systemically will target and eliminate antigen-expressing cells in the brain. A clinical example of this is the progressive brain autoimmune disease multiple sclerosis.

The complexity of the nervous system poses several challenging problems for scientists and clinicians who seek to apply gene therapy to neurological disorders [11]. In addition to the standard problems associated with gene therapy, we deal with very delicate, complex networks of cells and face the issue of accessibility and targeting the desired cell type(s) when considering gene therapy strategies in the central nervous system. Unlike other organs in the body such as the liver or lungs where large proportions of the organs can be damaged with minimal or no functional consequences, damage to extremely small areas of the brain can be devastating. Therapeutic targeting to selective areas or cell types will be difficult to achieve in the central nervous system (CNS).

Excluding the identified genetic causes of neurodegenerative diseases, the etiology underlying the primary neurological disorders is unknown. While the principle cell types affected in disorders such as Parkinson's and Alzheimer's have been identified, the exact contributing factors or conditions that trigger relentless neuronal degeneration are presently unknown. Therefore, at this time, gene products that help to reduce the effects of neural dysfunction, offset neuronal death, inhibit apoptosis, or encourage cell survival form the basis of gene therapy in the nervous system. As gene therapy approaches are developed and refined, the outcome of gene therapy in the nervous system could be extremely effective.

Conclusion

Parkinson's disease is a progressive degenerative condition, generally characterized by trembling, slow motions, stiffness and abnormalities in body posture. In its most serious form, it is associated with a deep physical and mental disorder. Etiology and pathophysiology of this disease is relatively poorly understood and diagnoses are usually based on clinical features.

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Volume 2 Issue 6 June 2019

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